Concerning the Calcium and Potassium Level in Blood Serum in Physiological and Pathological Conditions.

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Klinicheskaia Meditsina (USSR), 15: 1: 90-98, 1937.

Calcium and potassium have a prominent role in human physiology; the level of these electrolytes in the blood can have a substantial clinical importance. Unfortunately, the use of the data, concerning the calcium and potassium level in the blood, is hindered by a lack of a clear depiction of, first, what we must consider a physiological norm, and second, what amounts of the electrolytes are characteristic for the different pathological conditions.

We shall only concern ourselves with the general quantities of calcium and potassium in the blood. During recent years, an interest has grown immensely in the ionized fraction of the mineral salts, especially of calcium which has, evidently, a more active physiological role. McLean and Hastings gave a formula by which it is possible to determine the ionized calcium contents in blood serum even more accurately than by the direct method. This formula shows that the ionized calcium contents of the blood is a function of the aggregate quantity of proteins in the blood. For its part, there exists a very close correlative tie between the proteins of the blood and total calcium; this is stated by many authors. From this, it follows that between total calcium and ionized calcium must also exist a close relationship. Actually, for example, Herbert's parallel data, concerning the total calcium and the diffused calcium in different pathological conditions, give a correlation coefficient of 0.98 for both quantities. In this way, regardless of the fact that only the ionized calcium is active, while all of the calcium is not, the determination of the total calcium does not lose its practical importance.

Concerning the question of the physiological norms of calcium, prior to Jensens work there were only contradictory data based on single observations and dissimilar methods which in 2 or 3 instances gave quantities that did not correspond to each other. The calcium norm data published after 1918 are brought together in the recenly published Ehrstrom monograph. Including also, several works published in the last two years, we collected 52 norms (for the period 1918-1935 inclusively).

The first thing of this that strikes the eye is the nonconformity of the separate norms between themselves. These discrepancies can be partially explained by the difference of the methods adopted, but even by similar methods, the discrepancies between the separate authors prove to be so marked that the highest limitation of one norm never exceeds the lower limitation of the other. Thus, by the DeBoard method, the highest limitation of the Billingheimer norm comprises 9.6 mg%, but the Leithher norm, found in the same year and in almost the same number of people, only begins with 10.6 mg%. By the Kramer and Tisdall method, the Likint

norm ends at 10.5 mg%, but the Rosen and Krasnov norm begins at 10.7 mg%, etc.

Another characteristic trait of the calcium norms is a very large fluctuation amplitude of their upper and lower limitations. By a majority of the standard norms, fluctuations within the limitations of 1.5-2 mg% are considered physiological. Ehrstrom, on the basis of his dynamic investigations of calcium variation during a day, considers 8.2 and 12 mg% as the extreme points; in other words, he establishes the fluctuation range of the normal calcium level at 3.8 mg%.

The literature on the potassium norms is incomparably poorer. Having supplemented Thomasson's data, we were able to collect only 14 potassium norms. And here we meet extremely differing figures, even in those instances when they were received on relatively large groups of healthy subjects. The fluctuational range of the physiological limitations by one and the same author is still wider than for calcium. Kramer and Tisdall compute the variance of the potassium content from 18 to 22 mg% as physiological, ie, within a range of 4 mg%. The range of normal fluctuations of Ol'mer, Paian and Berteaux attain 10 mg%.

The clinical importance of the electrolytic levels in the blood is extremely depreciated by this variety of figures being given as a norm; depending on the choice of one or another of the figures, the level of the electrolytes in a given person can be recognized as either normal or pathological.

The wide range of the physiological norm's extreme limitations creates a hindrance in the clinical use of these indices. The wider the zone of the physiological fluctuations of a given criterion, the smaller the number of cases that fall outside the limits of the norm, and the more seldom the given criterion can serve as an index of an organism's pathological condition.

The literature on the question of the potassium and calcium in the different diseases is very voluminous, but is distinguished also by an extreme inconsistency; that is explained, first of all, by the small number of observations of the separate pathological conditions; besides that, on many diseases there are no comparative investigations made by the same method and in the same laboratory. Ehrstrom, summing up his nearly exhaustive review of literature on calcium which encompassed 15 groups of different diseases, comes to the following conclusions. " Data concerning the mutual relationship of the blood serum's calcium in the different diseases vary to a high degree. One and the same diseases are characterized by first a normal quantity, and then by a lower quantity, and again by a higher quantity. The quantities received by the different authors for the same diseases can give a variance of up to 10 mg%." The same can be said in relation to the potassium.

The inadequacy of the status of the problem concerning the calcium and potassium levels in physiological and pathological conditions justifies our attempt to return to this problem on the basis of massive data and an exact statistical preparation of them.

For our material, we used the determinations of calcium and potassium in the blood serum of various patients who had applied for treatment with lysates during the 1933-1934 period.

In all, for the given time interval, calcium determinations were made from 1,945 patients (of these, 705 were examined prior to, and after the treatment); potassium determinations were made from 1,538 patients (509 were examined prior to, and after treatment).

The determinations were made by the same worker and by the same method; the calcium was determined by the DuBoard method and the potassium by the Kramer and Tisdall Method; the blood was taken from the ulnar vein with an empty stomach, after a 48 hour diet without animal proteins; the determinations in the blood serums were made at 9-10 a.m.. We, in this way, have a completely uniform material. Examining our material by the separate diseases, we are easily convinced that there is not one disease which would be characterized by an absolute predominance of indisputably high or indisputably low figures of calcium or potassium. In any disease there is encountered high, medium and low levels of the electrolytes, whereupon the medium levels and those near to them predominate, rather than the extreme levels. Thus, if we agree to consider the average values for calcium at 9.5-11.5 mg%, and for potassium at 18-22 mg%, then in these ranges, from any of the 20 groups of the investigated diseases, are found 78-94 % of the calcium observations and 75-91 % of the potassium observations.

Correspondingly, the mean arithmetical levels of the calcium and potassium differ very little from each other in the different diseases. For calcium, the maximum variance between the averages (psoriasis and neoplasm) amounts to 0.36 mg%, for potassium (ovarian-menustrative disorder and adiopsis) - 1.25 mg%.

To check the stability in the different averages being compared, we used a statistical test in the form of the so-called average error of difference. The average error of difference is computed by the formula:

$$\sigma = \sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}$$

σ = the calculated variance.

N = the quantity of statistical series being compared.

It is considered that the difference between the arithmetical averages of the two series (M_0-M_1) may be considered entirely proved and stable when it does not exceed more than three times its average error. It turns out that the difference in the averages do not in a single case exceed their error by more than three times. It is evident that in a sufficiently large number of observations, the distribution curves of the calcium and potassium levels in various diseases have more of a congruity than a difference, and are distinguished from each other only by secondary (and not very stable) characteristics. We come, in this manner, to the conclusion that, in general, the calcium and potassium levels can hardly serve as a differential diagnostic medium for the separate diseases.

These negative conclusions are at variance with a great number of works related to the clarification of the question concerning the calcium and

potassium levels in the various diseases. One must remember, however, that we first applied a method of comparative study of these electrolytes in the separate diseases to a massive material, and that we also first used more accurate methods of statistical analysis of the data received.

The pathological conditions that are known to be connected with a disturbance of the equilibrium of the electrolytes under investigation are not included in the number of the diseases encompassed by our material; this must, it seems, constrict our conclusions a little. The scope of such diseases, however, is not large. McLean and Hastings, citing a summary of the diseases connected with the disruption of calcium exchange, consider it generally acknowledged that the calcium level is reduced only in hypoparathyroidism, hypoproteinism, child tetany, in several forms of nephritis and in several cases of rachitis. They consider a raised calcium level as indisputable only in hyperparathyroidism and hyperproteinemia. But a portion of these conditions are only signs which may be found in various diseases, and the nephritises, rachitis and tetany, by the data of these as well as other authors, are far from being always exclusively characterized by low calcium figures.

The next and practically more important question which we can illuminate on our material, is the question of the physiological norms of the calcium and potassium contents in blood serum. We have data concerning only pathological conditions, never the less, it is possible to propose a method by which these data can be used for the establishment of the physiological norms with greater success than the attempts at investigation of healthy subjects have had to date. The essence of the proposed method, which can be adapted not only to electrolytes, but also to any other laboratory index, is included in the following.

Any sufficiently large number of determinations of the electrolytic levels or other biochemical properties in the various pathological conditions gives series of figures of which one is located, known to us, beneath the unknown norm, and the others above it. Let us assume now that the entire group of patients were subjected to a repeat investigation on the electrolytic contents of the blood, after the successful use of any therapeutic measures. Let us suppose that these measures do not even give a full recovery, and we do not receive a complete normalization of the biochemical indices after the completion of the treatment; still, were this treatment in the majority of the cases, then we must expect that in the group of patients which prior to the treatment possessed lowered biochemical indices in comparison to the unknown physiological norm, a slight increaseof them will occur. On the other hand, a group of patients with raised levels of the same indices prior to treatment, must evidence a lowering of them after treatment. And only in the group of patients which possessed normal levels of the biochemical indices prior to the treatment, are the levels unchanged after successful therapy. Thus, by the observation of the dynamics of the biochemical indices prior to and after treatment in the same patients, we may approach the physiological norm which we must observe in a practically healthy person.

The proposed method of determining physiological norms possesses many advantages in comparison with the usual method of determining the norms on healthy subjects. We have already seen to what inconsistent and practically useless results these investigations of healthy people have led, in relation to the physiological calcium and potassium norms. It is possible to note several causes of this failure. One of them is contained in the difficulty of selecting truly healthy human material. Often, a circle of people, that is usually conveniently located, is used in the capacity of practically healthy people for the determination of the norms, without an intensified investigation of the actual condition of their health. Even with a special selection of the subjects from a number of the most healthy groups of students, military personnel and athletes, the inclusion of a small fraction of personnel in prepathological conditions and perhaps even in a condition of hidden disease is possible. In general, the line between health and disease in any given conditions can be drawn only conditionally, and this alone significantly hinders the selection of a subject group.

It is further necessary to allow for the possibility of physiological fluctuations in the level of the subject indices due to various factors. In relation to calcium, Ehrstrom, for example, established, with sufficient conclusiveness, the presence of fluctuations within the limits of 0.6-1.0 mg% from 8 a.m. to 6 p.m. in the healthy, and 0.6-2.6 mg% in the sick. Holmquist investigated the fluctuations of calcium in 5 normal people over a 24 hour period and found that the maximum contents of calcium occur during the sleep period, and the minimum at 1600 hours, during which, the amplitude between the extreme points comprise 3.4 mg%. The careful investigation of Cloetta, Fischer and Loeff showed, inversely, the lowering of the calcium and potassium by 9.9 and 16.6 % upon the change from wakefulness to sleep; it is true that this was under the influence of narcotics. We can consider that a marked increase of the calcium and potassium levels under the influence of an alarm, and a similar lowering of them under the influence of soothing has been indisputably established (Glaser, Cloetta and others). Even the character of the diet, evidently, cannot be regarded as having no influence on the level of the electrolytes, although the fact of eating itself, as the observations of many authors have shown, does not create changes in comparison with the determinations of calcium made on an empty stomach. All the listed factors (and probably many more) can be a cause of significant fluctuations of the electrolytic level in healthy persons if the test group is not placed under absolutely equal conditions. These unnoticeably included physiological fluctuations extend the limitations of the norm received on healthy people, and lessens its importance as a scale for the data received on sick people situated in different conditions.

The next weak spot of the usual method of establishing norms, is the numerical strength of the examined group. As we convinced ourselves from the literature review, norms are established on a negligible number of observations, and in those cases when the group being examined is increased in number, there rises the danger of including in it pathological subjects or persons with an altered level of electrolytes due to one or another of the physiological causes.

Last, the method of statistical processing of the acquired material is still another source of errors. Most frequently this material is not subjected to a processing at all, and the extreme points received by an investigation of a given group of healthy people are considered as the extreme limitations of the norm. It is sufficient to include in this group 2-3 subjects whose level of the biochemical index is lowered or raised by one reason or another, and the limitations of the norm are expanded, even if, in the majority of those being examined, the fluctuation is much more narrow.

The method being proposed by us, for the establishment of norms on pathological material, suffers much less from the listed inadequacies.

A collection of any given quantity of pathological cases presents no complication. The affair here is complicated by the circumstance that in a large number of observations it is easier to encounter sharp declinations from the norm. Conversely, the more diverse the circumference of the diseases encompassed, and the wider the-wider the fluctuational amplitudes of the individual observations, the more graphically the process of normalization of the indices under investigation will be brought out after treatment, and the more distinctly the limitations of the unchanged normal zone of the indices will be marked. All complications connected with the physiological causes of fluctuation in the level of the criterion being studied, are removed to an important degree by the fact that the clinical patients are usually investigated under similar standard conditions in regard time, diet etc. Any necessity to exclude the extreme readings in the selection of the norms extremities falls away, due to the fact that in our method of showing the norms, allobservations may be included without exception; and due to the fact that here the organism itself denotes that level of the biochemical index which is indicated on the way to recovery.

The establishment of physiologically normal levels of the electrolytes that are of interest to us, on pathological material, can serve as a concrete example of the use of our proposed method. For this purpose, we arrange repeated (prior to, and after treatment with lysates) determinations of calcium in 705 patients, and of potassium, in 509 patients. Besides that, in 506 of the patients , a twice repeated quota was calculated (prior to, and after treatment with lysates), i.e., the relation of the potassium level to the calcium level, to which several investigators attach greater clinical significance than to the absolute levels of both the electrolytes.

We shall attempt, first of all, to find the calcium norm. In table № 1, the aggregate of the observations is divided into groups by the height of the index prior to treatment and the resultant change of this index after treatment. The lower the calcium level prior to treatment, the stronger it rose after treatment. And, conversely, the highest readings prior to treatment, displayed the most acute drop. In the two largest groups, having 10.1-10.5 and 10.6-11.0 mg% of calcium prior to treatment, the change of the average levels was less, and did not exceed ± 2 %. It is completely natural to assume that within the limitations of these two groups, i.e., in the range of 10.1-11.0 mg%, are included the normal

figures of calcium which are not significantly changed in the process of the treatment.

(See table 1)

This conclusion, made on the basis of the dynamics of the average quantities per group as a whole, can be proved by a more detailed examination of the changes which took place within each group under the influence of the treatment. In the first four groups, with a calcium level of 8.1-10.0 mg%, there occurs, as a result of the treatment in the overwhelming majority (76%) of the cases, a raising of the level. In the last three groups, with a calcium level of 11.1-13.0 mg%, there is observed a reverse occurrence; here the cases in which the calcium level is lowered by the influence of the treatment (83%) are predominant.

In the two groups having a calcium level of 10.1-11.0 mg% prior to treatment, there is no such distinctness in the changes. This may be explained by the fact that we have here a zone of normal calcium levels where the therapeutic factor cannot create material changes, and where the fluctuations of the calcium level in different directions can be explained by the incidental influences of physiological causes which are unnoticed in the extreme groups with acutely pathological calcium figures.

In this manner the analysis and dynamics of the average measures, and the movement of individual levels point out the limitations of the normal calcium zone, namely, 10.1-11.0 mg%.

Analogous investigations in regards to potassium, and also the determination of the quota, lead to the conclusion that the normal potassium level lies between 19.1-20.0 mg%, and the norm of the quota is between 1.80-1.90.

However, the figures presented are only the rough limitations of the norms. We have found, thus far, only those intervals of the grouping within the limitations of which the therapeutic factor produces the least changes, and where, consequently, the physiological norm was located, but the boundaries of the true norm may prove to be inward of the selected interval.

It is therefor necessary to supplementally trace the dynamics of the individual electrolytic levels within the discovered normal zones. Dividing them into more minute intervals and subjecting the resultant data to the same analysis, we come to the following arrangement of narrow norms and even its own variety of central points to which the pathological deviations seem to gravitate as a result of treatment.

(See Table 2)

By absolute height, the norms found by us on the [illegible] material do not sharply differ from several published norms which were based on the changes of the electrolytic level in healthy subjects. Two recent investigations which were based on extensive material, namely the works

of Mull and Bill (207 healthy women). and Needels and Marborg (323 healthy people in ages 10-17) give the average amount of the calcium norm at 10.6 and 10.7 mg%, ie, amounts almost exactly coinciding with our data.

However, the basic characteristic of our norms and their main distinction from the norms of other authors consists of the fact that instead of a wide zone of the normal values for the levels of the electrolytes, we receive very narrow boundaries of the fluctuations of these levels (practically exact norms).

The wide limitations of the norms proposed by the majority of authors are conclusively disproved by our data. The much used Killeen (exact transliteration is "Kilin"-Tr) norms allow, for example, a fluctuation of the normal calcium level within the limits of 10.4-12.4 mg%. But, how can we consider the calcium levels within these boundaries as normal, if by our data, the same calcium level was found in 98 patients, and nearing the end of the treatment the level lowered in 81 of the patients? It is also expressly impossible to include in the normal zone, as do Jansen, Kramer & Tisdall and other authors, such low calcium levels as 9.1-10.0 mg%, because such calcium levels in the patients will rise in the overwhelming majority of cases; this would not take place if these were the physiologically normal levels. The same applies to potassium; the generally accepted norms of Killeen, Thomasson (exact transliteration is "Tomasson"-Tr), Kramer & Tisdall and other authors include such levels as 17.0-18.0 or 20.2-23.0 mg% which in 80 % of the sick cases will accordingly rise or fall after treatment.

Several logical considerations also speak for the necessity of the maximum contraction of the norms. If we stop on any of the broad norms and assume that for a healthy organism, it is of no consequence to have 18.0 or 23.0 mg% of potassium or 9.0-12.0 mg% of calcium in the blood, then why would 0.2-0.3 mg% outside of this borderline denote a pathological condition? And conversely, if we attach a significance to electrolytic changes in tenths of units beyond the limitations of the norm, then why must a change in the potassium and calcium level by several full units, within the limitations of the norm, be considered of no consequence for the biochemical balance of the organism? Would it not be more accurate to presume that there are, comparatively, very narrow borders of the physiological norm, something like the ideal mathematical point from which, both above and below, runs a continuous line of pathological changes in the electrolytic levels?

The recognition of a point norm need not be hindered by the circumstance that, practically speaking, we encounter more or less wide fluctuations of the electrolytic levels in the investigation of healthy subjects. The causes of the latter effect consist mainly of mistakes in the method and of inequalities in the conditions of the tests in the investigation of the separate subjects. The more uniform these conditions, and the more completely they encompass the various factors influencing the electrolytic level, the narrower the limits of the norm and the more the slight divergences from it may be considered as pathological.

Several observations remain to be made concerning the practical significance of the narrow electrolytic norms found by us.

If we were to compare our data of the distribution of the electrolytic levels in the different pathological conditions with several generally accepted and most substantiated wide norms, then we would receive the following results. With the calcium norms given by Killeen (10.4-12.4 mg%), Kramer and Tisdall (9.0-10.5 mg%), or Hall and Hill (10.0-11.5 mg%), 45-69 % of our cases prove to be within the limitations of these norms. For potassium, with the norms of Killeen (18.0-23.0 mg%), Thomasson (17.0-23.0 mg%) and Kramer & Tisdall (18.0-21.0 mg%), 68-92 % of 1538 pathological cases appear in the boundaries of these norms. An impression is created that the determination of the calcium and potassium in a patient's blood is deprived, in the majority of the cases, of any clinical significance what so ever.

The use of our narrow norms gives a different picture. With the calcium norm at 10.3-10.6 mg%, 74% of the cases prove to be beyond the limitations of this norm. With the potassium norm at 19.3-19.8 mg%, 83 % of the investigated cases show a pathological level of this electrolyte. By our point norms, the pathological divergences are 86 % of the cases by the calcium, and 95 % of the cases by the potassium. A systematic inspection of the level of both electrolytes in the various pathological conditions will thereby discover a definite clinical importance. True, deviations from a narrow norm will, in the majority of cases, be confined to comparatively narrow limitations. However, it is impossible to draw a principal division between the great and the small deviations from the norm. In both these and other cases, a completely definite movement of the electrolytic levels toward the norm is to be observed during the process of treatment. Consequently, even comparatively small deviations from the norm appears as a pathology, and a disappearance or a decrease of these deviations may be considered as an objective indication of a restoration of the disturbed equilibrium in the electrolytic metabolism. The more acute deviations from the norm probably have a more serious clinical significance; the slight deviations may be regarded as only a tendency to disrupt the balance of the electrolytes. Our narrow norms return the clinical and prognostic importance to these biochemical indices, which they almost lose with the generally accepted wide zones of the normal levels.

CONCLUSIONS

1. The physiological norms established by many authors for the calcium and potassium in the blood serum of healthy individuals are characterized by large discrepancies; besides that, in the majority of cases such wide ranges are given that the overwhelming portion of observations in pathological conditions also turn out to be in the limits of the norm; due to this, the practical significance in the use of these norms is being lost.

2. A variation-statistical analysis of the distribution curves of calcium and potassium in 20 different diseases bring us to the conclusion

that the level of these electrolytes can serve neither as a differential-diagnostic method nor as a reliable comparative characteristic of the separate diseases.

3. For the purposes of establishing and checking physiological norms, it is proposed to use a statistical analysis of the normalization process of the biochemical indices in a sufficiently large number of patients undergoing treatment by any active therapy.

4. On the material of 705 and 509 repeated calcium and potassium observations in sick individuals, we established narrow limitations of the physiological norm of these electrolytes, and also their proportions or quotas. These new norms are 10.3-10.6 mg % for calcium and 19.3-19.8 mg% for potassium and 1.83-1.86 for the quota.

5. 74 % and 85% of the calcium and potassium determinations made on the patients prove to be outside the limitations of the newly found norms; consequently, the determination of the level of electrolytes may have a significance in clinical practice.

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Table 1

Calcium level prior to treatment			Calcium level after treatment				
			No of cases				
By Group in mg%	average in mg%	no of cases	with an increase	with a decrease	no change	average in mg%	the change in %
8.0-8.5	8.20	1	1	-	-	10.80	+31.7
8.6-9.0	8.99	6	5	1	-	10.46	+17.7
9.1-9.5	9.34	19	18	1	-	10.54	+12.9
9.6-10.0	9.85	139	104	18	17	10.40	+ 5.6
10.1-10.5	10.30	186	102	53	31	10.53	+ 2.2
10.6-11.0	10.77	255	83	138	34	10.62	- 1.7
11.1-11.5	11.25	66	5	54	7	10.66	- 4.8
11.6-12.0	11.66	32	2	27	3	10.75	-7.3
12.6-13.0	12.60	1	-	1	-	10.60	-15.9
Total	10.45	705	320	293	92	10.56	- 1.1

Table 2

Electrolytes	Narrow Limitations of the norms	Central points of the norms
Calcium	10.3-10.6 mg%	10.5 mg%
Potassium	19.3-19.8 mg%	19.5 mg%
Quota	1.83-1.86	1.86